IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Robert C. SHIPMAN *et al.*
Title:	Materials and Methods for Analysis of ATP-Binding Cassette Transporter Gene Expression
Appl. No.:	10/582,982
International Filing Date:	December 15, 2004
§ 371(c) Date:	June 15, 2006
Examiner:	Steven C. Pohnert
Art Unit:	1634
Confirmation Number:	1560

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
P.O. Box 1450
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Sir:

This is an Appeal under 37 C.F.R. § 41.31 stemming from the final Office Action issued March 30, 2009, and the Advisory Action issued September 10, 2009. A Notice of Appeal was filed September 29, 2009. This Appeal Brief is filed in accordance with 37 C.F.R. § 41.37 together with the appeal fee. If the fee submitted herewith is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741. If an extension of time is required, Appellants hereby petition for such extension and authorizes the extension fee to be charged to the same deposit account.

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I. REAL PARTY IN INTEREST

The real party of interest is NoAb Biodiscoveries, Inc., the assignee of record of each inventor's entire interest.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no prior or pending appeals, judicial proceedings or interferences which are related to, may directly affect, or may be directly affected by or have a bearing on, the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 49, 50 and 78 are pending, finally rejected, and are the subject of this appeal.

New claims 86-89 presented in the after-final response filed August 28, 2009 have **not** been entered.

Claims 1-48, 51-77 and 79-85 are canceled.

IV. STATUS OF AMENDMENTS

The amendments included in the after-final response filed August 28, 2009, have **not** been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

As reflected in the independent claims, the claimed subject matter is directed to arrays comprising two or more nucleic acid probes useful for uniquely identifying nucleic acid molecules that encode different human ABC transporters. As taught in the specification, the claimed arrays are useful for simultaneously detecting the expression of up to all 48 ABC transporter genes known at the time of filing (depending on the number of unique probes present), and for identifying which specific ABC transporter genes are being expressed. *See, e.g.*, page 11, lines 12-18, of the specification as filed. Determining the ABC transporter gene expression profile in specific cells could be useful to designing and selecting specific drug treatment protocols that would be effective in the specific target cells. *See, e.g.*, page 2, lines 3-6, of the specification as filed. For example, knowing which specific ABC transporter genes are being expressed, or the overall pattern of ABC transporter gene expression, in target cells can be used to determine whether a particular drug might be effective for the patient at hand and/or whether a particular patient might be a suitable candidate for a specific drug therapy. *See, e.g.*, page 2, lines 6-11, of the specification as filed. The claimed arrays are useful in carrying out such studies.

The claims on appeal include two independent claims, claim 49 and claim 78.

Claim 49 is directed to an array comprising two or more nucleic acid molecules immobilized on a substrate, wherein at least two of the nucleic acid molecules have a nucleic acid sequence consisting of SEQ ID NO:12, 15, 21, 22, 23, 24, 25, 26, 35 or 44. This subject matter is described in the specification as filed, for example, at pages 3, 5-6, 16, and 22-23. In particular, page 5, line 29, to page 6, line 1, page 22, lines 25-32, and page 23, lines 22-29, discuss arrays generally. Page 2, lines 21-33, and page 16, lines 11-18, describe sets (arrays) of at least two nucleic acid molecules. Page 3, lines 1-13, and page 16, lines 19-21, teach that the recited sequences may be used in such arrays.

Claim 78 is directed to an array for screening a sample for the presence of nucleic acid molecules that encode human ABC transporters, the array comprising a substrate having immobilized in distinct spots thereon at least 10 nucleic acid probes. This subject matter

likewise is described in the specification as filed at pages 3, 5-6, 16, 22-23 and 25. Again, page 5, line 29, to page 6, line 1, page 22, lines 25-32, and page 23, lines 22-29, discuss arrays generally. Page 25, lines 21-23 teaches that the nucleic acid molecule may be immobilized in distinct spots on an array. Page 2, lines 21-33, and page 16, lines 11-18, describe sets (arrays) of at least 10 nucleic acid molecules. Claim 78 further defines 10 of the probes by SEQ ID NO, as follows, with support for each probe given in parenthesis:

1) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 12. **[page 7, lines 31-32]**
2) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B4, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 15. **[page 8, lines 5-6]**
3) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B11, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 21. **[page 8, lines 17-18]**
4) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 22. **[page 8, lines 19-20]**
5) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C2, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 23. **[page 8, lines 21-22]**
6) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C3, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 24. **[page 8, lines 23-24]**
7) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C4, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 25. **[page 8, lines 25-26]**
8) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C5, wherein the nucleotide sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 26. **[page 8, lines 27-28]**

9) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter D1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 35.[1] **[page 9, lines 13-14]**

10) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter G2, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 44. **[page 9, lines 31-32]**

[1] Appellants note a typographical error in the listing of claim 78 submitted with the response filed August 28, 2009, where "ABC transporter 01" should be "ABC transporter D1." Claim 78 as newly presented in the response filed October 11, 2007 (and as presented in subsequent responses) correctly recites that SEQ ID NO:35 specifically hybridizes to a nucleic acid sequence encoding human "ABC transporter D1."

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole ground of rejection to be reviewed on appeal is whether the subject matter of claims 49, 50 and 78 is obvious under 35 U.S.C. §103(a) in view of (i) WO 02/46458 ("Denefle"); (ii) Dean *et al, J. Lipid Res.*, 42: 1007-17 (2001) . ("Dean"); (iii) WO 02/071928) ("Monahan"); (iv) WO 00/18912 ("Schmitz"); (v) GenBank Accession Number AC069137.6 (GI:14589784); (vi) WO 01/62977 ("Boyd"); (vii) GenBank Accession Number U63970.1 (GI:1764161); (viii) WO 02/74979 ("Wan"); (ix) WO 99/49735 ("Kruh"); (x) GenBank Accession Number Z31010.1 (GI:479155), and (xi) EP 1 074 617 A2 ("Ota").

VII. ARGUMENT

A. The Rejection Under 35 U.S.C. § 103(a) Is Improper

Claims 49, 50 and 78 are rejected under §103(a), as allegedly being obvious over the following references: (i) WO 02/46458 ("Denefle"); (ii) Dean *et al, J. Lipid Res.*, 42: 1007-17 (2001) . ("Dean"); (iii) WO 02/071928) ("Monahan"); (iv) WO 00/18912 ("Schmitz"); (v) GenBank Accession Number AC069137.6 (GI:14589784); (vi) WO 01/62977 ("Boyd"); (vii) GenBank Accession Number U63970.1 (GI:1764161); (viii) WO 02/74979 ("Wan"); (ix) WO 99/49735 ("Kruh"); (x) GenBank Accession Number Z31010.1 (GI:479155), and (xi) EP 1 074 617 A2 ("Ota"). This rejection is improper because no combination of the cited references would have suggested to a skilled artisan arrays comprising the specific ABC transporter gene probes recited in the instant claims, as required for a rejection under 35 U.S.C. § 103.

1. The Claimed Invention

As reflected in the pending independent claims, the present invention is directed to arrays comprising two or more nucleic acid molecules immobilized on a substrate, wherein at least two of the nucleic acid molecules have a nucleic acid sequence consisting of SEQ ID NOs:12, 15, 21, 22, 23, 24, 25, 26, 35 or 44 (claim 48) or to arrays comprising a substrate having immobilized in distinct spots thereon at least 10 nucleic acid probes, wherein 10 of the probes have nucleic acid sequences consisting of SEQ ID NOs:12, 15, 21, 22, 23, 24, 25, 26, 35 and 44 (claim 78). Such arrays are not taught or suggested by the cited references.

At the outset, Appellants note their disagreement with the Examiner's interpretation of the transitional phrase "having," explained in the Advisory Action dated September 20, 2009 ("Advisory Action"). The Examiner maintains that the "use of the broad 'have' followed by the narrow 'consisting of' results in a broad claim interpretation." Advisory Action at 5. Appellants disagree. As stated in MPEP § 2111.03, "[t]ransitional phrases such as 'having' must be interpreted in light of the specification to determine whether open or close language is intended." Moreover, the same section of the MPEP cites to *Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l., Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001), for the proposition that the "term 'having' in transitional phrase 'does not create a presumption that

the body of the claim is open.'" Indeed, the Federal Circuit in *Crystal Semiconductor* states that "the term 'having' does not convey the open-ended meaning as strongly as 'comprising.'" *Id.*

Claim 49 recites that "at least two of the nucleic acid molecules have a nucleic acid sequence consisting of SEQ ID NO: 12, 15, 21...." In this context, it is clear that the term "have" is intended to be a closed term. The phrase "consisting of" follows the phrase "nucleic acid sequence" in the body of the claim. Thus, the closed language conveyed by "consisting of" modifies the term "nucleic acid sequence." *See* MPEP § 2111.03 ("When the phrase 'consists of' appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole."). Claim 49 therefore should be interpreted as reciting probes consisting of the recited nucleic acid sequences.

Appellants do not believe that the language of claim 78 leaves any room for doubt as to the "closed" nature of the recited sequences. This claim recites ". . . at least 10 nucleic acid probes, wherein 10 of the probes consist of:..." specified sequences.

In addition to the claim structure itself, Appellants point to the specification for proper construction of claims 49 and 78. All of the claimed sequences and all of the sequences disclosed in the application for use as probes in an array, are less than 900 nucleotides in length. None of the examples of sequences to be used in an array as disclosed in the application include full-length ABC transporter genes. Moreover, full-length ABC transporter gene sequences would not be suitable for use as probes on an array due to their length. Thus, when claims 49 and 78 are read in the context of the claim language itself, and the specification, the nucleic acid sequences claimed should not be construed as broadly as the Examiner asserts.

2. The Teachings of the Cited References

The Final Office Action of March 30, 2009 ("Final Office Action") admits that the cited references do not teach the specific probes recited in the claims, *e.g.*, probes consisting of SEQ ID NOs:12, 15, 21, 22, 23, 24, 25, 26, 35 or 44. Final Office Action at 6. Thus, the obviousness inquiry should end here, as the cited references admittedly do not make out a

prima facie case of obviousness. *See* MPEP § 2141.03 ("All words in a claim must be considered in judging the patentability of that claim against the prior art.").

The Final Office Action nevertheless asserts that the claimed arrays are obvious, weaving a winding path from the teachings of the cited references to the claimed arrays that only could be maneuvered with the roadmap provided by the present application.

As taught in the specification, the recited probes are useful for uniquely identifying nucleic acid molecules that encode different human ABC transporters. Denefle is cited for teaching that the "characterization of new ABC genes will yield important transporter genes," and that its probes can be "immobilized on a support, . . . [and] ordered into matrices such as 'DNA chips.'" Final Office Action at 5. Dean is cited for teaching that "the ABC transporter family comprises 48 known ATP driven transporters, which have numerous important biological functions." *Id.* at 6. The other references are cited for teaching full-length ABC transporter gene sequences, including genomic sequences, that comprise the sequences of probes recited in the claims (*i.e.* SEQ ID NOs: 12, 15, 21, 23, 24, 25, 26, 35 and 44). The Final Office Action asserts that it would have been obvious to use the prior art sequences in the array of Denefle, and that "[t]he artisan would be motivated to combine the [prior art] sequences . . . because Dean teaches ABC gene transporters are important." *Id.* at 8. According to the Final Office Action, "the substitution or addition of the [prior art] sequences . . . would produce a microarray with probes equivalent to the recited SEQ ID NO." *Id.*

Apparently, the Examiner believes that because full-length ABC transporter gene sequences were known, one of skill in the art would have been motivated to make an array of probes useful for identifying the expression of specific genes, and such a (fictional) array would be functionally equivalent to the claimed arrays, thereby rendering the claimed arrays obvious. Appellants respectfully disagree on several grounds.

3. The References Provide No Guidance Or Reason To Make An Array As Claimed

The cited references do not provide any guidance or motivation, or reveal any reason, to make an array as claimed. The claims of the present application are directed to arrays which contain specified nucleic acid sequences which are between 488 and 810 nucleotides in

length and are capable of simultaneously distinguishing between members of the human ATP-binding cassette transporter gene family. Claims 49 and 78 are not directed towards individual oligonucleotides, but rather to a combination of sequences that each specifically hybridize to an individual ABC transporter gene. The cited art does not provide any teaching, suggestion or motivation to prepare an array of probes containing the exact sequences recited in claims 49 and 78, each of which is capable of uniquely identifying one of the 48 known human ABC transporter genes, in combination as part of an array, as provided by the present invention.

Because the cited references are wholly lacking any teaching or guidance that would have led the skilled artisan to the claimed invention, and do not provide any motivation or reason to select the recited sequences, the obviousness rejection is improper and should be withdrawn.

4. Full-Length Sequences Do Not Render The Claimed Probes Obvious

The full-length prior art sequences do not render obvious the specific probes recited in the instant claims. As noted above, there is simply no teaching in the cited references that would have led a skilled artisan to select a probe having the specific sequences recited in the claims.

In further support of their position, Appellants refer to several "unpublished" Board decisions which are instructive on the issue of the non-obviousness of probes, in view of known full-length sequences. The Examiner states that the reliance on such non-precedential decisions are "inappropriate as they are not precedential and thus are [*sic*] do not set precedent for examination of the appeal process." Advisory Action at 5. While these decisions are not binding, they do illustrate the application of valid legal principles to relevant fact patterns, and so provide useful guidance.

At the outset, Appellants recognize that knowledge of a full-length sequence may render obvious an undefined "probe" for that sequence, or a probe defined only by, for example, length and hybridization. *See, e.g., Ex parte Bandman*, Appeal No. 2003-1805; Application No. 09/079,892 (unpublished). The instant claims, however, are not so broad,

but instead recite probes consisting of specific sequences, as described *supra*. Under such circumstance, the specifically defined probes are not obvious unless there is a "particular recognition or suggestion of the specific sequences" in the cited art. *Ex parte Kolberg*, Appeal No. 97-2532; Application No. 08/427,569 (unpublished) at 9.

In *Kolberg*, the Examiner had based the obviousness rejection on the published full-length sequence and general knowledge about making hybridization probes. *Id.* at 6-7. Similar to the Office Action here, the Examiner's Answer had "[s]imply opin[ed] that 'any oligonucleotide probe from the HTLV-1 sequences of [the prior art] are deemed functionally equivalent to the claimed oligonucleotides' . . . without a factual basis." *Id.* at 9. The Board reversed the rejection, finding the record "insufficient to establish a conclusion of obviousness." *Kolberg*, page 9.

Although *Kolberg* was decided prior to *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (U.S. 2007), it invokes the principles of *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), which the Federal Circuit has cited post-*KSR* for differentiating "between proper and improper applications of 'obvious to try.'" *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). As noted in *Kolberg,* the only way for the skilled artisan to arrive at specifically defined probes when the cited art provides no suggestion of the specifically claimed sequences is to "'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.'" *Kolberg* at 9 (citing *O'Farrell* 853 F.2d at 903). This same passage of *O'Farrell* was cited this year by the Federal Circuit in *Kubin* as describing when "courts should not succumb to hindsight claims of obviousness." *Kubin*, 561 F.3d at 1359 (emphasis added). *See also Proctor & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009) (applying the principles of *O'Farrell u*nder the rubric of *KSR* to find a specific chemical compound non-obvious).

As noted above and recognized in the Office Action, the present record reveals no particular recognition of the significance of the claimed sequences, and no suggestion to design probes based thereon. Thus, as with the claims determined to be non-obvious in

Kolberg and *Proctor & Gamble*, the only way the skilled person might have arrived at the claimed invention was by "merely throw[ing] metaphorical darts at a board filled with combinatorial prior art possibilities;" the Federal Circuit has confirmed that such circumstances do not amount to obviousness under *KSR*. *Kubin*, 561 F.3d at 1359.

5. The Claimed Probes Are Not Equivalent To Full-Length Sequences

The Final Office Action alleges that "it would have been . . . obvious . . . to use the sequences taught [in the art] in the array taught by Denefle." Final Office Action at 7. However, there is no evidence that such an array would be functionally equivalent to the claimed array. As set forth above, the claimed arrays comprise probes that each uniquely identify a single ABC transporter gene out of a family of at least 48 human ABC transporter genes known at the time of filing. There is no evidence that the sequences in the art, which include full-length, genomic sequences, could perform this function. Indeed, such full-length sequences would not be suitable for use as probes on an array because of their length (thousands or tens of thousands of nucleotide bases) and likely regions of homology which would detect other members of the ABC transporter family leading to potential false positive signals on an array.

Another unpublished Board decision, *Ex parte Weichselbaum*, Appeal No. 1999-1458; Application No. 07/943,812 (unpublished), is instructive. At issue in that case was the patentability of a construct that included a radiation-responsive promoter. Constructs comprising the promoter were known, but not where the promoter was linked to a gene encoding a therapeutic peptide, as claimed. According to the Examiner, the radiation-inducibility was an inherent property of the promoter, and it would have been obvious to substitute one promoter for another. *Weichselbaum* at 6-7. According to the Applicant, the radiation-inducibility was an unexpected property that was not taught or suggested by the cited art. *Weichselbaum* at 7. The Board determined that the record did not support the rejection because there was no evidence that the prior art promoters that had been linked to genes encoding therapeutic peptides were radiation-responsive. *Weichselbaum* at 9. Thus, there was no evidence that the prior art promoters were, in fact, "equivalent." *Id.*

In the present case, there is no evidence that any array based on the known ABC transporter genes would be functionally equivalent to the claimed array, *e.g.*, would be useful for identifying specific ABC transporter gene(s) out of a family of at least 48 human ABC transporter genes known at the time of filing. Thus, the obviousness rejection is improper and should be withdrawn.

6. The Claimed Probes Cannot Be Held Obvious Over Fictional Prior Art

The present record also reveals no specific probes or arrays of probes to which the claimed arrays, which comprise specifically defined probes, might be functionally equivalent. Thus, the doctrine of "functional equivalence" cannot be applied to the pending claims. As stated in MPEP § 2144.06, "[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." Here, there is no recognition that the claimed arrays or probes are functionally equivalent to prior art arrays or probes. Indeed, no specific prior art arrays or probes have been identified. In essence, the invention has been rejected over hypothetical, fictional prior art that does not even exist.

In addition to being contrary to law, this rejection places Appellants in the impossible position of needing to establish that the claimed arrays of probes are not functionally equivalent to fictional probes, whose specific properties and functions cannot be ascertained, tested or compared. Indeed, MPEP § 716.02(e) expressly states that "applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art" (emphasis added). The MPEP cites *In re Chapman*, 357 F.2d 418 (CCPA 1966), for the proposition that "[r]equiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention . . . 'would be requiring comparison of the results of the invention with the results of the invention,'" which is exactly what Appellants were improperly asked to do here.

The Examiner maintains that no such requirement was made. *See* Advisory Action at 7. However, the Examiner has specifically suggested that "a declaration demonstrating unexpected results, would be the easiest way to overcome the art of record." Interview

Summary, November 10, 2008. Since there is no specific array with specific ABC transporter probes in any of the cited art, Appellants are indeed being asked to compare the claimed invention with subject matter that does not exist.

Appellants nonetheless attempted to address this issue in the Declaration of Dr. Robert C. Shipman, Ph.D. filed January 21, 2009, in which inventor Dr. Shipman compared the claimed probes to probes that resulted from the use of known primer selection computer programs, when used to generate probes based on the ABC transporter genes corresponding to the probes recited in the claims. In performing this analysis, Dr. Shipman used information that would not have been available to the skilled artisan without knowledge of the present application, such as the target PCR product sizes which Dr. Shipman set to correspond to the size of the claimed probes. Shipman Declaration, ¶ 16. Even then, the program did not identify the claimed probe sequences or even sequences that were equivalent thereto. As Dr. Shipman explains, the data obtained indicate that the claimed probes would be better at identifying their targets under stringent conditions than the comparison probes. Shipman Declaration, ¶ 17, Thus, Dr. Shipman concludes that commonly used primer design software does not generate probes that would be functionally equivalent to the recited probes. Shipman Declaration, ¶ 18.

The Examiner alleges that the Declaration is not persuasive because, allegedly, the skilled artisan would have undertaken the same steps that the present inventors took to arrive at the present invention, *e.g.*, the same verification, validation and selection steps. *See* Final Office Action at 3. This assertion is made without any support whatsoever, and again leaves Appellants tilting at windmills, because the record is simply devoid of any evidence of any motivation that would have led a skilled person to even attempt to design an array as claimed, let alone any of the parameters that might have guided such an undertaking. To the contrary, Dr. Shipman attested that "the prior art does not teach the necessary information that would allow a person skilled in the art to identify probe sequences such as the specific nucleic acid sequences found in the Application." Shipman Declaration, ¶ 15.

The Examiner also criticizes Appellants' evidence, stating that the "declaration has provided no experimental evidence that the claimed probes function as probes any better then probes that are obvious over the prior art of record." Advisory Action at 8. However, again

there is nothing in the art of record which describes a physical array containing probes to ABC transporter genes. Thus, Appellants are being asked to compare a hypothetical array to the subject matter of the claims on appeal. Of the thousands of possible arrays which could be produced, Appellants are uncertain which probes and arrays they should compare to the claimed arrays to provide the Examiner with the evidence he is unreasonably requiring.

7. The Claimed Invention Is Not "Obvious To Try"

Appellants also emphasize that the present invention cannot be considered "obvious to try," because the possible "solutions" to the problem of providing an array as claimed were not finite, identified, or predictable. The Examiner maintains that:

> the teachings of the prior art clearly indicate that there are 48 known ABC transporter genes with known sequences. Thus there are a finite number of possibilities with a reasonable expectation of success as one of skill in the art would be able [to] predictably design probes to known sequences.

Advisory Action at 6 (text in brackets added).

This assertion ignores the fact that the number of possible arrays based on the 48 known ABC transporter genes is virtually infinite. For example, there is a very large number of possible probes for each of the 48 genes, because the probes can be of widely different lengths and can be chosen from different regions of the gene. The number of possibilities increases exponentially when designing an array, because one of skill in the art making an array could chose any probe for one gene to use with any probe for another gene, etc. Even if there were only 10 possible probes for each gene, that would result in 1×10^{48} possible arrays. Focusing on the 10 probes recited in the claims, and assuming only 10 possible probes for each gene, the claimed array is still 1 out of a possible 10,000,000,000. This is a far cry from the finite number of "identified and predictable solutions" required by *KSR*.

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007), the court emphasized that obviousness requires that the prior art give a reason or motivation to make the specific composition claimed. *Takeda* at 1356. No art has been cited here which would have provided a reason or motivation to make the specific

probes recited in the claims and combine them in an array, as claimed. Thus, the obviousness rejection is improper, and should be reversed.

B. Conclusion

For at least the foregoing reasons claims 49, 50 and 78 are non-obvious and patentable over the art of record. Accordingly, reversal of the rejection is respectfully requested.

Respectfully submitted,

Date November 19, 2009 By _____

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VIII. CLAIMS APPENDIX

49. An array comprising two or more nucleic acid molecules immobilized on a substrate, wherein at least two of the nucleic acid molecules have a nucleic acid sequence consisting of SEQ ID NO:12, 15, 21, 22, 23, 24, 25, 26, 35 or 44.

50. The array according to claim 49, wherein the array is a microarray.

78. An array for screening a sample for the presence of nucleic acid molecules that encode human ABC transporters, the array comprising a substrate having immobilized in distinct spots thereon at least 10 nucleic acid probes, wherein 10 of the probes consist of:

1) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 12;
2) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B4, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 15;
3) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B11, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 21;
4) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 22;
5) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C2, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 23;

6) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C3, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 24;

7) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C4, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 25;

8) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C5, wherein the nucleotide sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 26;

9) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter D1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 35; and

10) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter G2, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 44.

IX. EVIDENCE APPENDIX

1. Declaration under 37 C.F.R. § 132 by Dr. Robert C. Shipman, Ph.D. executed January 19, 2009, originally filed January 21, 2009 and considered by the Examiner in the Final Office Action Dated March 30, 2009.

The following Board of Patent Appeal and Interference Decisions were provided to the Examiner with the Response dated August 28, 2009 and considered by the Examiner in the Advisory Action dated September 10, 2009.

2. *Ex parte Bandman*, Appeal No. 2003-1805 (unpublished)

3. *Ex parte Kolberg*, Appeal No. 97-2532 (unpublished)

4. *Ex parte Weichselbaum*, Appeal No. 1999-1458 (unpublished)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No	:	10/582,982 Confirmation No.: 1560
Applicants	:	Robert C. Shipman and David K. H. Lee
Filed	:	June 15, 2006
Title	:	Materials and Methods for Analysis of ATP-Binding Cassette Transporter Gene Expression
TC./A.U.	:	1634
Examiner	:	POHNERT, Steven C.
Docket No.	:	13516-4
Customer No.	:	001059

Honorable Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313–1450

Dear Sir:

DECLARATION UNDER 37 CFR §1.132

I, Robert C. Shipman, a citizen of Canada, and resident of Mississauga, Ontario, Canada, declare that the following facts are within my knowledge and are true.

1. I reside at 130 Vista Boulevard, Mississauga, Ontario, Canada L5M 1V9.

2. I currently am the Director of Genomics at NoAb Biodiscoveries Inc., 2820 Argentia Road, Unit 8, Mississauga, Ontario L5N 8G4.

3. I have been working in the area of molecular biology since 1980. My *curriculum vitae* is attached to this Declaration as Exhibit A.

4. I am an inventor of the subject matter as claimed in U.S. Patent Application No. 10/582,982, filed June 15, 2006 (hereafter "the Application").

5. I have read and understood the disclosure and claims of the Application.

6. I have read and understood the Office Action that issued on the Application on August 7, 2008. The Examiner is of the view that claims 49, 50, and 78 are obvious under 35 USC § 103(a) over Denefle et al (WO02/46458) in view of Dean et al (J. Lipid Research, 2001, 42:1007-1017); Monahan et al (Wo02/071928); Schmitz (WO00/18912); GenBank AC069137.6; Boyd et al (WO01/62977); GenBank U63970.1; Wan et al (WO2002/74979); Kruh et al (WO99/49735); GenBank Z31010.1; and Ota et al (EP1074617A2).

7. I have read and understood the claims that are attached to this Declaration as Exhibit B that were filed on October 28, 2008 in response to the Office Action dated August 7, 2008. My comments below are based on the amended claims in Exhibit B (hereinafter "the amended claims").

8. The amended claims are limited to a combination of nucleic acid sequences that each specifically hybridize to one ABC transporter gene.

9. Denefle teaches nucleic acids corresponding to various exons of ABC transporter genes ABCA5, ABCA6, ABCA9, and ABCA10 genes as well as cDNAs encoding the novel full length of ABCA5, ABCA6, ABCA9, and ABCA10 proteins. Denefle also mentions that the invention described therein includes nucleotide probes and primers hybridizing with a nucleic acid sequence located in the region of any one of ABCA5, ABCA6, ABCA9, and ABCA10 nucleic acids (genomic DNA, messenger RNA, cDNA), and that these probes may be immobilized on a support.

10. Dean is a journal article that reviews the current state of knowledge on all

human ABC genes in inherited disease and drug resistance.

12. Monahan, Schmitz, GenBank AC069137.6, Boyd, GenBank U63970.1, Wan, Kruh, GenBank Z31010.1 and Ota describes the full length gene sequence for ABC transporter B1, B4, B11, C1, C2, C3, C4 and C5 (both in Kruh), D1 and G2, respectively.

13. None of the cited documents teach or suggest the any one of the nucleic acid sequences consisting of SEQ ID NO: 12, 15, 21, 22, 23, 24, 25, 26 35 or 44 as claimed in claim 49 of the amended claims. Further, none of the cited documents teach or suggest an array comprising a substrate and, immobilized thereon, in distinct spots, at least 10 nucleic probes consisting of SEQ ID NOS: 12, 15, 21, 22, 23, 24, 25, 26 35 and 44 as claimed in claim 78 of the amended claims.

14. The Examiner contends that the claimed SEQ ID NOS are obvious over the cited art, absent secondary considerations, because "[t]he substitution or deletion of the sequences taught [in the cited art] in the arrays taught by Denefle would produce a microarray with probes equivalent to the recited SEQ ID NO by replacing or adding known ABC transporter gene sequences for another. The artisan would have a reasonable expectation of success as methods of synthesizing nucleic acids and making arrays as well as the sequences of ABC transporter genes were known at the time of the invention".

15. I agree that methods of synthesizing nucleic acids and making arrays were known in the art at the time we made this invention, however, I disagree with the Examiner's submission that "there are many internet web sites that provide free downloadable software to aid in the selection of probes drawn from genetic data recorded in a spreadsheet". To my knowledge, no such programs exist. While the prior art may teach parameters and objectives involved in the selection of pcr primers and provide software for the selection of relatively short

oligonucleotides such as *pcr primers*, the prior art does not teach the necessary information that would allow a person skilled in the art to identify probe sequences such as the specific nucleic acid sequences found in the Application.

16. To verify that the known pcr primer selection programs do not provide the sequences claimed in the amended claims, we have accessed the widely used, and freely available, PCR primer design program called Primer3 (http://frodo.wi.mit.edu) and asked it to provide sets of primers and PCR products for each of the ABC transporter genes, B1, B4, B11, C1, C2, C3, C4, C5, D1 and G2. Using the default parameters, Primer3 does not return any of the PCR primer sequences or PCR products reported and claimed in the Application. Primer3 preferentially returns short (<300 bp) PCR products since this is the most efficient size for PCR/Taq polymerase processing rates and reduced mis-incorporation of base pairs. We then changed the default Primer3 parameters to obtain PCR product sizes in the same range as those in the Application, and Primer3 still did not return the PCR primer sequences or PCR product sequences reported and claimed in the Application.

17. To verify that the PCR products identified using Primer3 are not equivalent to those taught in the application we ran BLAST searches for both the Primer3 PCR products (obtained using the non-default product size range) and the PCR products from the Application. Below is a table containing the results. As can be seen, the numbers were higher (i.e. better) for the sequences from the Application. The values shown for each gene represent the values from the highest quality match in the BLAST search record (first line, highest identity match to the entire query sequence). The higher the number the better the match between the sequences and the better the chance that, under stringent hybridization conditions, the sequence will act as a probe for that sequence.

	BLAST Results for Sequences from the Application		BLAST Results for Sequences from Primer3	
ABCT Gene	Max Score	Total Score	Max Score	Total Score
B1	1420	1553	672	767
B4	1425	1618	724	724
B11	1328	1382	856	856
C1	1191	1405	616	616
C2	1462	1462	563	563
C3	1303	1303	688	688
C4	1433	1433	883	883
C5	1166	1166	836	836
D1	881	881	848	848
G2	1126	1126	884	884

18. The results shown in the Table above, show that freely available web-based PCR primer design software [ie. Primer3] does not generate probes or sequences that are equivalent to the ones that are claimed in the amended claims. Therefore the claimed sequences are in no way predictable based on the teachings of the cited art.

19. In further support of the unpredictability of the sequences that are claimed in the amended claims, it should also be noted that PCR primers that have been designed *in silico* to produce a single PCR product will frequently generate multiple PCR products in practice. In arriving at the present invention, almost every computer-generated PCR primer set had to be modified or redesigned using my experience and knowledge, at least once to obtain a sequence that worked in practice.

20. Still further, in arriving at the present invention, there were many examples of PCR primers that produced a single PCR product that, when cloned and sequenced, was not the gene it was designed to amplify. Again, using my experience and knowledge, the primer sequences had to be modified or

redesigned. There was also an occurrence where the PCR primers produced a single product that, when cloned, was lethal to the cells being transfected and transformed.

21. The examples described in Items 19 and 20 underline the assertion that there is no way to predict that any given PCR product will be a functional probe for a chosen nucleic acid sequence. In all cases, sequences selected using computer programs need to be verified and validated and in almost all cases, the experience, knowledge and skill of a senior scientist is required to obtain a sequence that, when reduced to practice, provides the desired probe product and performance in gene expression analyses.

22. In summary, I believe that we are entitled to claim the combination of nucleic acid sequences that each specifically hybridize to one ABC transporter gene that is found in the amended claims because these sequences are in no way predictable based on the teachings of the cited art and the knowledge of a person skilled in the art. This is because, using the teachings of the cited art, a person skilled in the art would not obtain products that would function as probes for the ABC transporter genes and therefore would not obtain products that are equivalent with the claimed sequences.

23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Application or patent resulting therefrom.

Jan. 19. 2009
Date

Robert C. Shipman, Ph.D.

EXHIBIT A

Curriculum Vitae

I. Degrees/Theses:

B.Sc. (1980) The University of British Columbia
A Common Leukemia-Associated Antigen in Human Acute Myelogenous Leukemia.

M.Sc. (1982) The University of British Columbia
Isolation of a Cell Surface Antigen specific for Human Acute Myelogenous Leukemia Cells.

Ph.D. (1987) The University of British Columbia
Characterization of a Common Myelogenous Leukemia-Associated Antigen (CAMAL) in Human Myelogenous Leukemia.

II. Previous Employment:

October 1987- July 1990
Project Leader, Inflammation and Cytokines Research Group,
Biotechnology K681.506, Pharma Research,
CIBA-GEIGY AG, Basel, Switzerland.

August 1990- July 1995
Lab Director and Project Leader, Molecular Oncology,
University Hospital Research Center (Zentrum fuer Lehre und Forschung),
KANTONSSPITAL BASEL, Basel, Switzerland.

September 1995- January 1996
Lab Director, Medical Genetics,
Division of Cellular and Molecular Biology,
ONTARIO CANCER INSTITUTE, Toronto, Ontario, Canada.

January 1996- August 1999
Project Manager-Molecular Pathology (p53/Brca1/Brca2),
Project Manager-Infectious Disease (Drug Resistant Tuberculosis),
Senior Scientist,
VISIBLE GENETICS INC., Toronto, Ontario, Canada.

June 2000- Present
Director- Genomics,
NOAB BIODISCOVERIES INC., Mississauga, Ontario, Canada

III. Professional societies:

1. American Association of Cancer Research (AACR)

2. American Association of Pharmaceutical Scientists (AAPS)

3. Collaborative Health Research Projects (CHRP) Grant Selection Committee Member 2003-2005
Collaborative Health Research Projects (CHRP) Grant Selection Committee Chair 2006

4. Canadian Institutes of Health Research (CIHR) Institute of Genetics Advisory Board Member 2004-2007

IV. Patents:

1. Method and Reagents for testing for mutations in the BRCA1 gene
(Issued June 11, 2002 - US6403303).

2. Method for single tube sequencing of nucleic acid polymers
(Issued July 4, 2000 – US6083699).

V. Invited presentations/seminars:

1. Allelic loss and alteration of tumour suppressor genes in human lung and bladder carcinoma. 10th Annual Meeting of the OAO/GTOR (Upper Rhine Oncology Association),
1994, Basel, Switzerland.

2. Alterations of putative tumour suppressor genes in human non-small cell lung carcinoma (NSCLC). 26th Annual Meeting of the USGEB/USSBE (Swiss Union of Biological Sciences), 1994, Bern, Switzerland.

3. Preferential allelic loss of the catalase gene (CAT) at 11p13 in human non-small cell lung cancer. Swiss Society for Oncology, 1994, Bern, Switzerland.

4. Preferential allelic loss of the CAT locus at chromosome 11p13 and the isolation of genes involved in the development of non-small cell lung cancer. C.R. Brupbacher Foundation 2nd Scientific Symposium: Genetic Predisposition to Cancer, 1995, Zurich, Switzerland.

5. Development of a stratified approach for the detection of gene mutations in genomic DNA of patient samples. Gene Mutational Analysis, Cambridge HealthTech Institute, September 30-October 1, 1996, Baltimore MD.

6. Analysis of putative tumour suppressor genes in human lung and bladder cancer. 5th

Annual Seminar on Molecular Pathology: DNA technology in the Clinical Laboratory, Beaumont Pathology Conferences, March 8-9, 1996, Royal Oak MI.

7. Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. Toronto Molecular Pathology/Molecular Diagnostics Group, Sunnybrook Health Sciences Centre, July 31, 1997, Toronto, Ontario.

8. Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. Association for Molecular Pathology Annual Meeting, November 12-15, 1997, San Diego CA.

9. Industrial applications of molecular biology. Genetics Technology post-diploma program, The Michener Institute for Applied Health Sciences, March 12, 1998, Toronto, Ontario.

10. Molecular applications in Biotechnology. Introduction to molecular DNA techniques, The Michener Institute for Applied Health Sciences, June 26, 1998, Toronto, Ontario.

11. Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. 3rd Annual New Cancer Strategies: P53, Cambridge Healthtech Institute, September 16-17, 1998, Washington DC.

12. Rapid detection of antibiotic resistance-associated mutations in 10 gene targets in Mycobacterium tuberculosis using the OpenGene system. Third Annual Conference on Microbial Genomes, The Institute for Genomic Research, January 29-February 1, 1999, Chantilly VA.

14. Industrial applications of molecular biology. Genetics Technology post-diploma program, The Michener Institute for Applied Health Sciences, March 10, 1999, Toronto, Ontario.

15. Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. 50th Annual Meeting of the Canadian Association of Pathologists, June19-22, 1999, Calgary, Alberta.

16. Molecular applications in Biotechnology. Introduction to molecular DNA techniques, The Michener Institute for Applied Health Sciences, June 25, 1999, Toronto, Ontario.

17. Rapid detection of antibiotic resistance-associated mutations in 12 gene targets in Mycobacterium tuberculosis using the OpenGene system. 20th Annual Congress of the European Society of Mycobacteriology, July 4-7, 1999, Lucerne, Switzerland.

VI. Publications:

1. A.Kh. Al-Rammahy, R. Shipman, A. Jackson and J.G. Levy (1980). Evidence for a common leukemia-associated antigen in human acute myelogenous leukemia.
Cancer Immunol. and Immunother. 9: 181-185.

2. A.J. Malcolm, R. Shipman and J.G. Levy (1981). Detection of a tumour-associated antigen on the surface of human acute myelogenous leukemia cells.
J. Immunol. 128: 2599-2603.

3. A.J. Malcolm, P.M. Logan, R. Shipman, R. Kurth and J.G. Levy (1983). Analysis of human myelogenous leukemia cells in the fluorescence-activated cell sorter using a tumour-specific antiserum.
Blood 61: 858-866.

4. R. Shipman, A.J. Malcolm and J.G. Levy (1983). Partial characterization of a membrane antigen which exhibits specificity for cells of patients with acute myelogenous leukemia.
Br. J. Cancer 47: 849-852.

5. A.J. Malcolm, R. Shipman, P.M. Logan and J.G. Levy (1984). A monoclonal antibody to myelogenous leukemia: isolation and characterization.
Exp. Hematol. 12: 539-547.

6. R. Shipman and J.G. Levy (1988). Expression of a leukemia-associated antigen (CAMAL) in four myeloid leukemia cell lines.
Leukemia Res. 12: 537-543.

7. J.K. Lazdins, T. Klimkait, K. Woods-Cook, M. Walker, E. Alteri, D. Cox, N. Cerletti, R. Shipman, G. Bilbe and G. McMaster (1991). HIV-1 lymphocytotropic restriction is overcome by TGF-□, an enhancer of viral expression in mononuclear phagocytes.
J. Immunol. 147: 1201-1207.

8. J.K. Lazdins, T. Klimkait, E. Alteri, M. Walker, K. Woods-Cook, D. Cox, G. Bilbe, R. Shipman, N. Cerletti and G. McMaster (1991). TGF-□: upregulator of HIV replication in macrophages.
Res. Virol. 142: 239-242.

9. G. Bilbe, J. Delabie, J. Bruggen, H. Richener, F.A.M. Asselbergs, N. Cerletti, C. Sorg, K. Odink, L. Tarcsay, W. Wiesendanger, C. DeWolf-Peeters and R. Shipman (1992). Restin, a new class of intermediate filament-associated protein highly expressed in the Reed-Sternberg cells of Hodgkin's disease.
EMBO J. 11: 2103-2113.

10. J.Delabie, R. Shipman, J. Bruggen, B. De Strooper, F. Van Leuven, L.Tarscay, N. Cerletti, K. Odink, V. Diehl, G. Bilbe and C. De Wolf-Peeters (1992). Expression of the novel intermediate filament-associated protein "restin" in Hodgkin's disease and anaplastic large cell lymphoma.

Blood 80: 2891-2896.

11. P. Schraml, R. Shipman and C.U. Ludwig (1993). cDNA subtraction library construction using a magnet-assisted subtraction technique (MAST).
Trends Genet. 9 (3): 70-71.

12. R. Shipman, P. Schraml, M. Colombi, G. Raefle and C.U. Ludwig (1993). Loss of heterozygosity on chromosome 11p13 in primary bladder carcinoma.
Hum. Genet. 91: 455-458.

13. S.Park, M. Schalling, A. Bernard, S. Maheswaran, G.C. Shipley, D. Roberts, J. Fletcher,
R. Shipman, J. Rheinwald, G. Demetri, J. Griffin, M. Minden, D.E. Housman and D. Haber (1993). The Wilms tumor gene WT1 is expressed in mesoderm-derived tissues and mutated in mesothelioma.
Nature Genet. 4: 415-420.

14. C.U. Ludwig, M. Gencik and R. Shipman (1993). Multistep transformation in low grade lymphoproliferative diseases.
Annals Oncology 4: 825-830.

15. R. Shipman (1994). Applications of the polymerase chain reaction to tumour analysis and diagnosis. In: Klapdor, ed. Current Tumor Diagnosis: Applications, Clinical Relevance, Research, Trends.Cancer of the Lung- State and Trends in Diagnosis and Therapy.
Munich, W. Zuckerschwerdt Verlag GmbH, pp. 839-845.

16. R. Shipman and P. Schraml (1995). Reverse Transcription PCR (RT-PCR) from total RNA. In: PCR Applications Manual. Boehringer Mannheim GmbH. pp. 87-94.

17. R. Shipman and P. Schraml (1995). Analysis of p53 point mutations using PCR.
In: PCR Applications Manual. Boehringer Mannheim GmbH. pp. 158-160.

18. R. Shipman and P. Schraml (1995). Detection of allelic loss in tumour tissue genomic DNA by amplified fragment length polymorphism PCR (AFLP-PCR) using variable number tandem repeat (VNTR) sequence primers or microsatellite sequence primers. In: PCR Applications Manual. Boehringer Mannheim GmbH. pp. 161-165.

19. P. Schraml, R. Shipman, M. Colombi and C.U. Ludwig (1994). Identification of genes differentially expressed in normal lung and non-small cell lung carcinoma tissue.
Cancer Res. 54: 5236-5240.

20. A. Juretic, G.C. Spagnoli, H. Horig, R. Shipman, T. Kocher, F. Harder and M. Heberer (1995). Tyrosine kinase dependent and independent events induced by IL-2 stimulation: IL-2 mediated NO production required for the induction of LAK cell activity in rat splenocytes is tyrosine kinase dependent.

Immunology 85: 325-330.

21. P. Schraml, R. Shipman and C.U. Ludwig (1996). Screening cDNA Libraries: Isolating the 5' end of a cDNA from a lambda cDNA library with PCR.
Focus (Life Technologies Inc.) 18 (2): 38-39.

22. R. Shipman, P. Schraml, M. Colombi, E. Schultheiss, G. Raefle, P. Dalquen and C.U. Ludwig (1996). Frequent p53 gene alterations (mutation, allelic loss, nuclear accumulation) in primary non-small cell lung cancer.
Eur. J. Cancer 32A: 335-341.

23. R. Shipman, P. Schraml, H. Moch, M. Colombi, G. Sauter, M.J. Mihatsch and C.U. Ludwig (1997). p53 protein accumulation and p53 gene alterations (RFLP, VNTR and p53 gene mutations) in non-invasive versus invasive human transitional bladder cancer.
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24. R. Shipman, P. Schraml, M. Colombi and C.U. Ludwig (1998). Allelic deletion at chromosome 11p13 defines a tumour suppressor region between the catalase gene and D11S935 in human non-small cell lung carcinoma.
Int. J. Oncology 12: 107-111.

25. R. Shipman and J. Dunn (1998). Fluorescence-based automated DNA sequencing.
Biomedical Products 23 (5): 38-40.

26. M.E. Saunders, R. MacKenzie, R. Shipman, E. Fransen, R. Gilbert and R.C.K. Jordan (1999). Patterns of p53 gene mutations in head and neck cancer: Full-length gene sequencing and results of primary radiotherapy.
Clin. Cancer Res. 5:2455-2463.

27. P.C.M. Larsson, B. Beheshti, H.A Sampson, M.A.S. Jewett and R. Shipman (2001). Allelic deletion fingerprinting of urine cell sediments in bladder cancer.
Mol. Diagnosis 6:181-188.

28. P.C.M. Larsson, B. Beheshti, R. Shipman and M.A.S. Jewett (2001).
Allelic deletion analysis of multiple bladder tumors.
UroOncology 1:291-295.

VII. Abstracts presented at conferences:

1. R. Shipman and J.G. Levy (1981). Isolation and Partial Characterization of a Leukemia-Associated Antigen on the Surface of Human Acute Myelogenous Leukemia Cells. Proceedings of the International Symposium on the Cellular and Molecular Biology of Hematopoetic Stem Cell Differentiation. Ontario Cancer Institute and the National Cancer Institute. Honey Harbour, ON.

2. R. Shipman, A.J. Malcolm and J.G. Levy (1981). Detection and Isolation of a Leukemia-Associated Antigen on the Surface of Human Acute Myelogenous Leukemia Cells. Pacific Northwest Immunology Group Meeting. The Fred Hutchinson Cancer Institute. Friday Harbour, San Juan Island, WA..

3. R. Shipman, P.M. Logan, V. Lum and J.G. Levy (1984). Isolation of a Common Myelogenous Leukemia-Associated Antigen and its Detection in Human Myelogenous Leukemia Cells using Immunoperoxidase. ICN/UCLA Symposium on Molecular and Cellular Biology: Leukemia 1985. Keystone, Colorado, USA.

4. R. Shipman and J.G. Levy (1986). Characterization of a Common Myelogenous Leukemia-Associated Antigen (CAMAL) from Human Myelogenous Leukemia Cells. 6th International Congress of Immunology. Toronto, ON.

5. J. Lazdins, E. Alteri, M. Walker, K. Woods-Cook, Th. Klimkait, D. Cox, G.Bilbe, R. Shipman, N. Cerletti and G. McMaster (1990). Role of TGFb in HIV-1 replication in macrophages. Franco-German Cooperation on AIDS Research Symposium: Macrophages as Target Cells of HIV. Freiburg im Breisgau, Germany.

6. J. Lazdins, E. Alteri, M. Walker, K. Woods-Cook, D. Cox, G. Bilbe, R. Shipman, N. Cerletti and G. McMaster (1990). TGFb upregulation of HIV replication in macrophages. 27th Annual Meeting of the Society for Leukocyte Biology. Heraklion-Crete, Greece.

7. R. Shipman, P. Schraml, G. Raefle and C.U. Ludwig (1991). Deletions of putative tumour suppressor genes in human non-small cell lung carcinoma. AACR Special Conference: Negative controls on cell growth and their breakdown during the pathogenesis of cancer. Chatham, MA.

8. T. O'Reilly, S. Kunz, R. Shipman, L. Tarcsay and G. Bilbe (1992). In Vivo induction of cytokine mRNA following administration of liposomal MTP-PE (CGP 19835A) to mice.
32nd ICAAC, American Society for Microbiology. Anaheim, CA.

9. R. Shipman, P. Schraml, M. Colombi, G. Raefle, P. Dalquen and C.U. Ludwig (1993). p53 mutations in human, primary non-small cell lung carcinoma. C.R. Brupbacher Foundation First Scientific Symposium: p53 in Growth Control and Neoplasia. Zurich, CH.

10. R. Shipman, P. Schraml, M. Colombi, and C.U. Ludwig (1994). Allelic loss and alteration of tumour suppressor genes in human lung and bladder carcinoma. 10th Annual Meeting of the OAO/GTOR (Upper Rhine Oncology Association). Basel, CH.

11. R. Shipman and C.U. Ludwig (1994). Allelic deletion, mutation and expression of putative tumour suppressor genes in human non-small cell lung carcinoma. Keystone Symposia on Molecular and Cellular Biology: Molecular Basis of Cancer Therapy.

Tamarron, CO.

12. R. Shipman, P. Schraml, M. Colombi, and C.U. Ludwig (1994). Alterations of putative tumour suppressor genes in human non-small cell lung carcinoma (NSCLC). 26th Annual Meeting of the USGEB/USSBE (Swiss Union of Biological Sciences). Bern, CH.

13. R. Shipman, P. Schraml and C.U. Ludwig (1994). Preferential allelic loss of the catalase gene (CAT) at 11p13 in human non-small cell lung cancer. Swiss Society for Oncology, Bern, CH.

14. P. Schraml, R. Shipman and C.U. Ludwig (1994). Differentially expressed genes in normal lung and non-small cell lung cancer. Swiss Society for Oncology. Bern, CH.

15. R. Shipman, P. Schraml, and C.U. Ludwig (1995). Preferential allelic loss of catalase and alterations to the p53 and WT1 genes in primary non-small cell lung cancer. 86th Annual Meeting of the AACR. Toronto, ON.

16. Shipman, R., P. Schraml, and C.U. Ludwig (1995). Preferential allelic loss of the CAT locus at chromosome 11p13 and the isolation of genes involved in the development of non-small cell lung cancer. C.R. Brupbacher Foundation Second Scientific Symposium: Genetic Predisposition to Cancer. Zurich, CH.

17. P. Schraml, R. Shipman and C.U. Ludwig (1995). Identification and characterisation of genes down-regulated in non-small cell lung cancer. C.R. Brupbacher Foundation Second Scientific Symposium: Genetic Predisposition to Cancer. Zurich, CH.

18. M.E. Saunders and R. Shipman (1997). Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. 3rd Annual Meeting of the Association for Molecular Pathology, San Diego, CA.

19. R. Shipman and M.E. Saunders (1998). Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens.
American Association for Cancer Research Annual Meeting, New Orleans, LA.

20. M.E. Saunders, R. Shipman and R.C.K. Jordan (1998). Complete p53 gene analysis in head and neck cancer: Mutation detection in genomic DNA from archival specimens. American Association for Cancer Research Annual Meeting, New Orleans, LA.

21. R. Shipman and M.E. Saunders (1998). Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. 4th Annual Meeting of the Association for Molecular Pathology, Crystal City, VA.

22. R. Shipman and M.E. Saunders (1998). Complete p53 gene analysis using the OpenGene system: Mutation detection in genomic DNA from archival and fresh clinical specimens. 48th Annual Meeting of the American Society for Human Genetics, Denver, CO.

23. M.E. Saunders, R. MacKenzie, R. Shipman, E. Fransen, R. Gilbert and R.C.K. Jordan (1998). Full-length p53 gene sequencing in head and neck cancer and outcome radiation therapy. 22nd Annual Meeting of the Eastern Great Lakes Head and Neck Association, Toronto, ON.

24. R. Shipman (1999). Complete p53 mutation analysis, allelic loss and microsatellite instability in non-small cell lung cancer. American Association for Cancer Research Annual Meeting, Philadelphia, PA.

25. M.E. Saunders, R. MacKenzie, R. Shipman, E. Fransen, R. Gilbert and R.C.K. Jordan (1999). Full-length p53 gene sequencing in head and neck cancer and outcome radiation therapy. American Association for Cancer Research Annual Meeting, Philadelphia, PA.

26. D. Nuesca, S. Jacob, F. Jamieson, G. Broukhanski and R. Shipman (1999). Rapid detection of antibiotic resistance-associated mutations in 10 gene targets in Mycobacterium tuberculosis using the OpenGene system. 99th General Meeting of the American Society for Microbiology, Chicago, IL.

27. R. Shipman (1999).Complete p53 mutation analysis, allelic loss and microsatellite instability in non-small cell lung cancer. 50th Annual Meeting of the Canadian Association of Pathologists, Calgary, AB.

28. D. Nuesca, S. Jacob, F. Jamieson, G. Broukhanski and R. Shipman (1999). Rapid detection of antibiotic resistance-associated mutations in 12 gene targets in Mycobacterium tuberculosis using the OpenGene system. 50th Annual Meeting of the Canadian Association of Pathologists, Calgary, AB.

29. M.E. Saunders, R. MacKenzie, R. Shipman, E. Fransen, R. Gilbert and R.C.K. Jordan (1999). Full-length p53 gene sequencing in head and neck cancer and outcome radiation therapy. 50th Annual Meeting of the Canadian Association of Pathologists, Calgary, AB.

30. R. Shipman, S. Carmichael, S. Fung and T. Ewart (2001). The Affect of Hybridization Conditions on Fluorescent Signal Intensities Recovered from Microarrays. 7th Annual Meeting of the Society for Biomolecular Screening, Baltimore, MD.

31. R. Shipman, S. Fung, A. Tang, S. Carmichael and T. Ewart (2003). APTarray: An Acquired Pathogen Titre Array for the Determination of Serum Antibody Levels. 9th Annual Meeting of the Society for Biomolecular Screening, Portland, OR.

32. R. Shipman, E. Rose, K. Marseu, J. Sidhu and D.K.H Lee (2005). Gene Expression Analysis of Drug Treated Cell Lines using a Human ABC Transporter Microarray. AAPS

Workshop on Drug Transporters in ADME: From the Bench to the Bedside. Parsippany, NJ.

33. R. Shipman, E. Rose, K. Marseu, J. Sidhu and D.K.H Lee (2005). Gene Expression Profiling using a Human ABC Transporter Microarray. American Association for Cancer Research Annual Meeting, Anaheim, CA.

34. R. Shipman, E. Rose, K. Marseu, J. Sidhu and D.K.H Lee (2005). A Microarray for ABC Transporter Gene Expression Profiling. Cambridge Healthtech Institute Microarrays in Medicine. Boston, MA.

35. J. Morrison, J. Sidhu, D.K.H. Lee and R. Shipman (2006). DTEx™ - Gene Expression Profiling using a Human ABC Transporter Microarray. World Microarray Congress. Vancouver, BC.

36. R. Shipman, J. Morrison, J. Sidhu and D.K.H. Lee (2007). Time Course Analysis of Drug Transporter, Cytochrome P450 and Nuclear Receptor Gene Expression Profiles in 21 Day Caco-2 Cell Cultures. AAPS Workshop on Drug Transporters in ADME: From the Bench to the Bedside. North Bethesda, MD.

37. J. Morrison, J. Sidhu, D.K.H. Lee and R. Shipman (2007). Analysis of Drug Transporter, Cytochrome P450 and Nuclear Receptor Gene Expression Profiles in Human Hepatocytes. AAPS Workshop on Drug Transporters in ADME: From the Bench to the Bedside. North Bethesda, MD.

38. R. Shipman, J. Morrison, J. Sidhu and D.K.H. Lee (2007). Expression Profiling of Drug Transporter, Cytochrome P450 and Nuclear Receptor Genes in Caco-2 Cells using DTEx™ Microarrays. DDI-2007, 10th International Conference on Drug-Drug Interactions: Scientific and Regulatory Updates and DDI Technologies in Depth: Enzyme Inhibition, Enzyme Induction and Drug Transporter Interactions. Institute for Scientific Exchange. Bellevue, WA

VIII. Operating Grants and Fellowships:

1981 B.C. Cancer Foundation Studentship.

1982 Graduate Student Research Assistantship.

1983 University Graduate Student Fellowship.

1984 University Graduate Student Fellowship.

1991 Grant #31-30098.90 (SFr 215,819).
Deletions and mutations of putative tumour suppressor genes in human non-small cell lung cancer. Swiss National Research Fund (Schweizerischer Nationalfonds zur

Foerderung
der wissenschaftlichen Forschung).

1992 Grant #AKT 318 (SFr. 40,000).
Cloning of putative tumor suppressor genes by subtraction hybridisation of normal lung tissue cDNA versus lung carcinoma cDNA of the same patient. Cancer Research Switzerland (Krebsforschung Schweiz).

1993 Grant #31-36494.92 (SFr 345,000).
Isolation of genes from chromosome 11p13, that are deleted in human non-small cell lung cancer, using a yeast artificial chromosome-based approach. Swiss National Research Fund (Schweizerischer Nationalfonds zur Foerderung der wissenschaftlichen Forschung).

1993 Grant # FOR 396 (SFr 160,000).
Characterisation of cDNAs expressed in normal human lung tissue and not in primary non-small cell lung carcinoma (NSCLC). Swiss Cancer League (Schweizerische Krebsliga).

IX. Teaching experience:

1982, Teaching assistant and Lab instructor. Undergraduate Microbiology Courses, Department of Microbiology, UBC, Vancouver, BC, Canada.

1983, Teaching assistant and Lab instructor. Undergraduate Microbiology Courses, Department of Microbiology, UBC, Vancouver, BC, Canada.

1984, Teaching assistant and Lab instructor. Undergraduate Microbiology Courses, Department of Microbiology, UBC, Vancouver, BC, Canada.

1994, Course instructor. PCR course for clinical researchers (May 19-20), Boehringer Mannheim AG (Switzerland), Laborschule ZLF, Kantonsspital Basel, Basel, Switzerland.

1995, Course instructor. PCR "trouble-shooting" Workshop (March 9-10), Boehringer Mannheim AG (Switzerland), Laborschule ZLF, Kantonsspital Basel, Basel, Switzerland.

EXHIBIT B

1. – 48. (Previously Cancelled)

49. (Currently Amended) An array comprising two or more nucleic acid molecules immobilized on a substrate, wherein at least two of the nucleic acid molecules have a nucleic acid sequence consisting of ~~the nucleic acid sequence as shown in~~ SEQ ID ~~NOS~~ NO:12, 15, 21, 22, 23, 24, 25, 26, 35 or 44.

50. (Previously Amended) The array according to claim 49, wherein the array is a microarray.

51 – 77. (Previously Cancelled)

78. (Previously Amended) An array for screening a sample for the presence of nucleic acid molecules that encode human ABC transporters, the array comprising a substrate having immobilized in distinct spots thereon at least 10 nucleic acid probes, wherein 10 of the probes consist of:

1) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 12;
2) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B4, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 15;
3) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter B11, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 21;

4) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 22;

5) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C2, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 23;

6) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C3, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 24;

7) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C4, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 25;

8) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter C5, wherein the nucleotide sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 26;

9) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter D1, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 35; and

10) a probe that specifically hybridizes to a nucleic acid sequence encoding human ABC transporter G2, wherein the nucleic acid sequence of the probe is a nucleic acid sequence consisting of SEQ ID NO. 44.

79. – 85. (Previously Cancelled)

Paper No. 36

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte OLGA BANDMAN, JENNIFER L. HILLMAN, PREETI LAL, KARL J. GUEGLER, GINA GORGONE, NEIL C. CORLEY, CHANDRA PATTERSON, and MARIAH R. BAUGHN

Appeal No. 2003-1805
Application No. 09/079,892

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 25 through 28 and 33 through 37. Claims 6 through 12 are pending and have been allowed. Claims 29 through 32 are also pending but have been withdrawn from consideration by the examiner. Claims 25 and 33 are representative of the subject matter on appeal. Since claim 25 refers to allowed claim 7, we reproduce claims 7, 25, and 33 as follows:

7. An isolated and purified polynucleotide comprising a polynucleotide sequence as shown in SEQ ID NO:4, wherein said polynucleotide of SEQ ID NO:4 encodes a polypeptide having glutamine fructose-6-phosphate amidotransferase activity.

25. A method for detecting a target polynucleotide in a sample, wherein said target polynucleotide comprises the polynucleotide of claim 7, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

33. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:4,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

The examiner relies upon the following references:

Nishi et al. (Nishi '713)	5,876,713	Mar. 2, 1999
Eur. Pat. App. (Nishi EPA)	EP 824,149 A2	Feb. 18, 1998

Claims 33 through 37 stand rejected under 35 U.S.C. § 112, first paragraph (written description). Claims 25 through 28 and 37 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies upon Nishi '713 and Nishi EPA in the alternative. We reverse the written description rejection and affirm the obviousness rejection.

Background

The present invention involves human carbohydrate metabolism enzymes referred to by appellants as "CARM." Specification, page 5. As seen from claims 7, 25, and 33 reproduced above, the claims under review in this appeal involve the polynucleotide sequence as shown in SEQ ID NO:4 which is said to code for CARM-1. Id., page 19, lines 14 through 20. As explained:

> CARM-1 has chemical and structural similarity with human glutamine: fructose-6-phosphate amidotransferase (GI 183082). In particular, CARM-1 and human glutamine: fructose-6-phosphate amidotransferase share 78% identity. A fragment of SEQ ID NO:4 from about nucleotide 243 to about nucleotide 260 is useful, for example, as a hybridization probe. Northern analysis shows the expression of this sequence in various libraries, at least 51% of which are immortalized or cancerous and at least 46% of which involve immune response. Of particular note is the expression of CARM-1 in gastrointestinal, male and female reproductive, and nervous tissues.

Id., page 20, lines 4 through 11.

Discussion

1. Written description.

The examiner considers that claims 33 through 37 do not comply with the written description requirement of 35 U.S.C. § 112, first paragraph, since:

> The specification defines an 'allelic sequence' (see page 10) as an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered and that any given natural or recombinant gene may have none, one or many, allelic forms, and that common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, substitutions of nucleotides each of which may occur alone or in combination with the others one or more times in a given sequence. This definition does not provide any specific information about the structure of naturally occurring (alleles) variants of SEQ ID NO:4 (i.e. where are the regions within which mutations are likely to occur) nor discloses any function for naturally occurring variants. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:4 relates to the structure of any naturally

> occurring alleles. The general knowledge in the art concerning alleles does not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e. the sequence encoding SEQ ID NO:2) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Examiner's Answer, paragraph bridging pages 3 and 4.

The examiner also

> [F]ully acknowledges appellants' recitation of the structural limitations of the polynucleotides of claim 33 parts b) and d)-e). However, the polynucleotides as defined in claim 33 parts b) and d)-e) encompass a genus of polynucleotides that encompasses widely variant species, some having the same functions as the polypeptide of SEQ ID NO:1, some having unknown and distinctly different functions and some possibly having no function. While one of skill in the art, provided the polynucleotide sequence of SEQ ID NO:4, may be able to recognize variants of SEQ ID NO:4 with nucleotide sequence sharing 90% identity, one cannot recognize which of these variants occurs naturally and is thus encompassed by the genus of claim 33 part b). Therefore, the skilled artisan would not be able to recognize a member of the claimed genus of polynucleotides merely from its structural definition. This enormous genus will encompass a wide variety of polynucleotides with their own distinct properties. Because appellants have provided no functional limitation for the claimed polynucleotides, the single disclosed polynucleotide of SEQ NO:4 is not representative of the entire genus and one of skill in the art would not recognize that appellants were in possession of all polynucleotides comprising a naturally-occurring polynucleotide having at least 90% identity to SEQ ID NO:4 as encompassed by the claims.

Examiner's Answer, paragraph bridging pages 11 and 12.

The Federal Circuit discussed the application of the written description requirement to inventions in the field of biotechnology in University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), stating

that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials" Id. at 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

In reviewing this rejection, we note that the examiner has not rejected claim 8 under this section of the statute. Claim 8 reads:

8. An isolated and purified polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to the polynucleotide of SEQ ID NO:4, wherein said naturally occurring polynucleotide sequence encodes a polypeptide having glutamine-fructose-6-phosphate amidotransferase activity.

As seen, claim 8 differs from claim 33 b) which is the focus of the examiner's written description rejection in that it adds the limitation that the naturally occurring polynucleotide sequence encodes a polypeptide having glutamine-fructose-6-phosphate amidotransferase activity. Since the examiner has conceded that a claim having the scope of claim 8 complies with the written description requirement of 35 U.S.C. § 112, we do not find that the lack of a statement of function in claim 33 b) means that that portion of the claim lacks written descriptive support.

Claim 33 b) defines a genus of polynucleotides by way of two significant qualifiers. First, the polynucleotide of claim 33 b) must be "naturally occurring." Second, the polynucleotide of claim 33 b) must be "at least 90% identical to the polynucleotide sequence of SEQ ID NO:4." As explained in Lilly, a genus of polynucleotides can be described by a representative number of polynucleotides sharing common structural features which constitute a substantial portion of the genus. The examiner is correct in his analysis that claim 33 b) includes so-called nonfunctional alleles. However, those nonfunctional alleles must be "naturally occurring" and be at least "90% identical to the polynucleotide sequence of SEQ ID NO:4." In our view, these two limitations adequately describe the genus of polynucleotides encompassed by claim 33 b) without that claim further including a functional limitation.

We understand the examiner's concern that one may not recognize that a polynucleotide sequence having 90% identity with that of SEQ ID NO: 4 is "naturally occurring." However, that concern is more properly raised under a rejection under 35 U.S.C. § 112, second paragraph, rather than the written description requirement of the first paragraph.

The written description rejection is reversed.

2. Obviousness.

We initially note that appellants state that the claims are grouped together for the purposes of this rejection. Appeal Brief, page 5. Accordingly, we shall decide the issues raised in the Examiner's obviousness rejection as they pertain to claim 25. 37 CFR § 1.192(c)(7). We also note that the two Nishi references relied upon by the examiner appear to be the same. Thus, we shall consider the merits of the examiner's rejection as it is based upon Nishi '713.

Claim 25 is directed to a method for detecting a target polynucleotide said to comprise the polynucleotide of claim 7 in a sample. To this end, a sample is hybridized with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample. The probe will specifically hybridize to the target polynucleotide, if present, forming a hybridization complex. The presence or absence of the hybridization complex is an indication as to whether the sample contained the target polynucleotide.

The examiner has determined without dispute by appellants that Nishi '713 describes a polynucleotide encoding a carbohydrate metabolizing enzyme (glutamine:fructose-6-phosphate amidotransferase activity) that is 100% identical to the amino acid sequence set forth in SEQ ID NO:1 of this application. Examiner's Answer, page 6. The examiner has also determined, again without dispute by appellants, that Nishi '713 describes a polynucleotide sequence encoding that polypeptide that is 67.7% identical to the polynucleotide sequence set forth in SEQ ID NO:4 of this application. Id. The basis for the examiner's findings are the sequence comparison printouts

obtained as a result of an electronic search of sequence databases. As seen from the sequence search report dated December 14, 1999, U.S.-09-079-892-4.rng, pages 1-3 the polynucleotide sequence extending from nucleotide 99-2144 of SEQ ID NO:4 of this application is 100% identical to the coding sequence set forth in Nishi '713. See, e.g., Figs. 2A-2F and SEQ ID NO:5 of Nishi '713.

The examiner has concluded that it would have been obvious to a person of ordinary skill in the art to use any 20 contiguous nucleotides in the region of the polynucleotide sequence described in Nishi '713 as a probe in either a hybridization reaction or as part of a set of probes/primers in a PCR reaction to detect a target polynucleotide. Once again, appellants do not dispute this aspect of the examiner's position. Indeed, Nishi suggests as much, stating:

> The DNA encoding the protein or the partial peptide of the present invention can be cloned either by PCR amplification by using synthetic DNA primers having a partial nucleotide sequence of the DNA coding for the protein or by hybridization using the DNA inserted in a suitable vector and labeled DNA fragment or synthetic DNA coding for a part or full region of the protein or the partial peptide of the present invention. The hybridization can be carried out by the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989). When a commercially available DNA library is used, the instructions given in the accompanying manual can be followed.

Nishi '713, column 15, lines 54 through 65.

Where the appellants and the examiner part company in regard to the obviousness rejection has to do with whether claim 25 on appeal is "directed only to detecting the target polynucleotides, comprising the polynucleotides recited in claim [] 7 . . ." (Appeal Brief, page 12) or whether claim 25 is inclusive of "detecting any target polynucleotide which hybridizes to probes generated from the sequence of

Nishi. . .." (Appeal Brief, page 11) (emphasis in each original). Appellants urge that claim 25 must be read such that the claimed method detects only the polynucleotides recited in claim 7. We disagree with appellants' claim construction.

First, appellants' position does not take into account that claim 25 explicitly reads upon a negative result, i.e., the probe comprising at least 20 contiguous nucleotides will not hybridize to any nucleotide sequence in the sample. This is seen in that claim 25 b) includes detecting the absence of a hybridization complex. Since appellants have not contravened the basic premise of the examiner's obviousness rejection, i.e., it would have been obvious to one of ordinary skill in the art to use a probe comprising at least 20 contiguous nucleotides based upon the polynucleotide sequence described in Nishi '713 in a hybridization method, the performance of such a method that results in a negative result reads directly upon claim 25. Thus, the examiner's rejection can be sustained on this basis.

Second, we do not read claim 25 in the manner in which appellants do. In our view, claim 25 is not limited "only to detecting the target polynucleotides comprising the polynucleotides recited in claim [] 7 . . .." Appeal Brief, page 12. Once a probe comprising at least 20 contiguous nucleotides is constructed based upon the polynucleotide sequence described in Nishi '713, the use of that probe in a hybridization method will result in the hybridization complex being formed if the probe hybridizes to any polynucleotide sequence in the sample under the hybridization conditions used. Thus, an appropriately constructed probe based upon the polynucleotide sequence described in Nishi '713 will hybridize to a polynucleotide sequence such as that of Nishi

'713, that of SEQ ID NO:4 of this application or any other polynucleotide sequence having sufficient complementarity given the hybridization conditions used.

The examiner's obviousness rejection is affirmed.

The decision of the examiner is affirmed-in-part.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

Sherman D. Winters Administrative Patent Judge	)
William F. Smith Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Eric Grimes Administrative Patent Judge	)

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Paper No. 49

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JANICE A. KOLBERG
and MICHAEL S. URDEA

Appeal No. 1997-2532
Application No. 08/427,569[1]

ON BRIEF

Before WINTERS, SPIEGEL, and SCHEINER, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 17 through 36, which are all of the claims pending in this application.

The claimed invention is directed to sandwich hybridization assays for detecting HTLV-1 (claims 31-33), probes (claims 17-30) and kits (claims 34-36) therefore. Two

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[1] Application for patent filed April 24, 1995. According to appellants, this application is a continuation of application 08/130,150 filed September 29, 1993, now abandoned, which is a continuation of application 07/813,585 filed December 23, 1991, now abandoned.

types of probes are claimed, i.e., amplifier and capture probes. Each probe has a first segment, i.e., an oligonucleotide of defined nucleic acid sequence, which hybridizes to a complementary distinct, separate nucleic acid sequence of the HTLV-1, thereby "sandwiching" the HTLV-1 between the probes. The capture probe (claims 20-22) has a second segment of nucleic acids complementary to the nucleic acid sequence of a solid phase oligonucleotide which allows separation of the complex of the sandwiched HTLV-1 from unreacted assay components, while the amplifier probe (claims 17-19) has a second segment of nucleic acids complementary to a "connecting" oligonucleotide segment of a "multimer." Neither second segment is complementary to an HTLV-1 nucleic acid sequence. In addition to the "connecting" oligonucleotide, the multimer also contains multiple oligonucleotides which are complementary to a labeled oligonucleotide. Thus, hybridization between the amplifier probe and the multimer ultimately "amplifies" the amount of label attached to the sandwich HTLV-1 via hybridization between the multimer and the labeled oligonucleotide. Claims 23-26 and 27-30 are directed to sets of two or more amplifier probes having different first segments and sets of two or more capture probes having different first segments. The first segments of the amplifier and capture probes comprise sequences selected from SEQ ID NOs. 6-41 and SEQ ID NOs. 42-53, respectively.

Claims 23 and 31 are illustrative and read as follows:

23. A set of synthetic oligonucleotides useful as amplifier probes in a sandwich hybridization assay for HTLV-1, comprising at least two different oligonucleotide probes, wherein each oligonucleotide probe consists of:

a first segment having a minimum length of about 25 nucleotides and a maximum length of about 100 nucleotides which segment is at least 90% homologous to a segment of HTLV-1 nucleic acid, wherein said first segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS: 6-41; and

a second segment consisting of a nucleotide sequence which is at least 90% homologous to an oligonucleotide segment of a nucleic acid multimer wherein said second segment is not complementary to HTLV-1 nucleic acid;

and optionally one or more noncomplementary segments each consisting of a nucleotide sequence that is not complementary to HTLV-1 nucleic acid.

31. A solution sandwich hybridization assay for detecting the presence of HTLV-1 in a sample, comprising:

(a) contacting the sample with (i) amplifier probes comprising the set of synthetic oligonucleotides of claim 23 and (ii) a set of capture probe oligonucleotides wherein there is a molar excess of amplifier probes and of capture probes over analyte nucleic acid in the sample, wherein said set of capture probe oligonucleotides comprises at least two different oligonucleotides each of which consists of

a first segment having a minimum length of about 25 nucleotides and a maximum length of about 100 nucleotides which segment is at least 90% homologous to a segment of HTLV-1 nucleic acid, wherein said first segment comprises a nucleotide sequence selected from the group consisting of SEQ ID NOS: 42-53; and

a second segment consisting of a nucleotide sequence which is at least 90% homologous to an oligonucleotide bound to a solid phase wherein said second segment is not complementary to HTLV-1 nucleic acid;

and optionally one or more noncomplementary segments each consisting of a nucleotide sequence that is not complementary to HTLV-1 nucleic acid;

(b) contacting the product of step (a) with said oligonucleotide bound to the solid phase;

(c) thereafter separating materials not bound to the solid phase;

(d) contacting the bound product of step (c) with a nucleic acid multimer, said multimer comprising at least one oligonucleotide segment that is at least 90% homologous to the second segment of the amplifier probe polynucleotide [sic, oligonucleotide] and a multiplicity of second oligonucleotide segments that are at least 90% homologous to a labeled oligonucleotide;

(e) removing unbound multimer;

(f) contacting the solid phase complex product of step (e) with the labeled oligonucleotide;

(g) removing unbound labeled oligonucleotide; and

(h) detecting the presence of label in the solid phase complex product of step (g) and, thereby, detecting the presence of virus in the sample.

The references relied on by the examiner are:

Hogan et al. (Hogan) (published International Application)	WO 88/03957	June 2, 1988
Urdea et al. (Urdea) (published International Application)	WO 89/03891	May 5, 1989

Seiki et al. (Seiki), "Human adult T-cell leukemia virus: Complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA," Proceedings of the National Academy of Sciences, USA, Vol. 80, pp. 3618-3622 (June 1983).

Stratagene 1988 Catalog, p. 39 (Stratagene).

Ratner et al. (Ratner), "Nucleotide Sequence Analysis of Isolates of Human T-Lymphotropic Virus Type I of Diverse Geographical Origins," AIDS Research and Human Retroviruses, Vol. 7, No. 11, pp. 923-941 (November 1991).

ISSUES[2]

[2] The examiner withdrew the final rejection of claims 17-36 under 35 U.S.C. § 112, first paragraph, as lacking enablement (see answer, para. bridging pp. 7-8).

Claims 17-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner. Claims 34-36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner and further in view of Stratagene. We REVERSE both rejections.

In reaching our decision in this appeal we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's answer (Paper No. 42, mailed November 26, 1996) for the examiner's reasoning in support of the rejection and to the appellants' brief (Paper No. 41, filed September 26, 1996) and to appellants' reply brief (Paper No. 43, filed January 24, 1997)[3] for the appellants' arguments thereagainst.

OPINION

Urdea discloses a generic solution sandwich hybridization assay comprising (a) contacting a sample with (i) an amplifier probe having a first segment that is complementary to a first portion of a nucleic acid sequence of interest and a second segment that is complementary to a oligonucleotide unit of a nucleic acid multimer and (ii) a capture probe having a first segment that is complementary to a second, different portion

[3] After initially denying entry of appellants' reply brief in a communication mailed February 25, 1997 (Paper No. 44), the examiner later entered the reply brief "[i]n view of the new rules for entry of reply briefs which went into effect December 1, 1997, which require the entry of reply briefs" (see communication mailed December 12, 1997, Paper No. 47).

of the nucleic acid sequence of interest and a second segment that is complementary to an oligonucleotide bound to a solid phase; (b) contacting the product of step (a) with the oligonucleotide bound to the solid phase; (c) thereafter separating materials not bound to the solid phase; (d) contacting the product of step (c) with the nucleic acid multimer, wherein the multimer comprises at least one oligonucleotide that is complementary to the second segment of the amplifier probe and a multiplicity of second oligonucleotide units that are complementary to a labeled oligonucleotide;
(e) removing unbound multimer; (f) contacting the product of step (e) with the labeled oligonucleotide; (g) removing unbound labeled oligonucleotide; and (h) detecting the presence of label in the product of step (g) to detect the presence of the nucleic acid sequence of interest in the sample (see e.g., claim 12; pp. 3, 7, 24-27 and 31-32; Example 3, pp. 46-49). While Urdea exemplifies assays, reagents and kits for detecting hepatitis B virus, Neisseria gonorrhoeae and Chlamydia trachomatis, "Urdea does not teach the use of any HTLV-1 sequences nor a methodology for selecting any specific HTLV-1 sequences" (answer, p. 4, last sentence). In other words, Urdea does not disclose or suggest amplifier and capture probes having first segments selected from the group consisting of SEQ ID NOs. 6-41 and SEQ ID NOs. 42-53, respectively.

Seiki "reports the complete 9,032-nucleotide sequence of the proviral genome [of HTLV-1] cloned in •ATK-1" (p. 3618, sentence bridging cc. 1-2; Fig. 2) and points "out that

the predicted viral genome ... could be tentative, because the provirus analyzed ... is that integrated in leukemia cells" (p. 3622, c. 2, first full para.).

Hogan discloses a method for preparing probes for use in hybridization assays which

> comprises constructing an oligonucleotide that is sufficiently complementary to hybridize to a region of rRNA selected to be unique to a non-viral organism or group of non-viral organisms sought to be detected, said region of rRNA being selected by comparing one or more variable region rRNA sequences of said non-viral organism or group of non-viral organisms with one or more variable region rRNA sequences from one or more non-viral organisms sought to be distinguished" (abstract).

Ratner determined the sequences for nucleotides 1-5184, including the long terminal repeat (LTR), *gag*, protease gene, and *pol* sequences, of HTLV-1 isolates of Caribbean and African origin (abstract; p. 924, c. 1, para 3; Fig. 1) and stated that

> [t]he limited sequence variation among HTLV-1 isolates suggests that diagnostic assays should be useful in detecting virtually all substrains of the virus. The positions of sequence variation outlined here should assist in the design of future diagnostic reagents. [P. 939, c. 2, para. 2.]

Stratagene describes two advantages of kits, convenience and quality control.

According to the examiner, it would have been obvious (a) to identify conserved regions of the HTLV-1 sequence disclosed by Seiki or Ratner (b) using the "the methodology of selection of particular primers as taught by Ratner or Hogan" (c) "to solve the problem of specific detection of a variety of HTLV-1 species" using the hybridization assay of Urdea (d) "since Ratner states 'The limited sequence variation among HTLV-1

isolates suggests that diagnostic assays should be useful in detection [sic, detecting] virtually all substrains of the virus. The positions of sequence variation outlined here should assist in the design of future diagnostic reagents.' " (answer, p. 6). Thus, the dispositive issue is whether the "methodology of selection" of Ratner or Hogan (or any other applied prior art reference) discloses or suggests the claimed synthetic oligonucleotides comprising a first segment selected from SEQ ID NOs. 6-41 and from SEQ ID NOs. 42-53 suitable for use as amplifier and capture probes, respectively, in a solution sandwich hybridization assay for HTLV-1.

First, we note that neither appellants nor the examiner appear to appreciate that Hogan is directed to nucleic acid probes for non-viral organisms based on unique rRNA sequences (see e.g., p. 3, ll. 22-30) found in 5S rRNA, 16S rRNA and 23S rRNA (see e.g., p. 9; claim 5). Hogan expressly states, "With the exception of viruses, all prokaryotic organisms contain rRNA molecules including 5S rRNA, 16S rRNA, and a larger rRNA molecule known as 23S rRNA" (emphasis added, p. 9, ll. 5-8). There is no evidence of record establishing that HTLV-1 contains 5S rRNA, 16S rRNA and/or 23S rRNA. The examiner has not provided any fact-based or reasoned explanation of why one of ordinary skill in the art would have looked to Hogan's method of selecting non-viral probes for detecting non-viral organisms for guidance in selecting viral nucleic acid probes for

detecting a virus with any reasonable expectation of success of obtaining oligonucleotides comprising SEQ ID NOs. 6-53 as specifically claimed.

Second, the examiner has failed to point out, and we do not find, where Ratner provides any particular recognition or suggestion of the specific sequences, i.e., SEQ ID NOs. 6-53, required by the claimed invention.

None of Urdea, Seiki or Stratagene provide any particular recognition or suggestion of SEQ ID NOs 6-53 as required by the claimed invention. Therefore, in our view the examiner's rejection can be aptly characterized as an "obvious to try" rejection, i.e., obvious to try any nucleotide sequence contained within the 9,000-plus nucleic acid HTLV-1 genome. Simply opining that "any oligonucleotide probe from the HTLV-1 sequences of Ratner or Seiki are deemed functionally equivalent to the claimed oligonucleotides" (answer, p. 12), without a factual basis supporting that opinion, is insufficient to establish a conclusion of obviousness. As stated in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)

> ... what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted).

Accordingly, we find the examiner has not carried his burden of establishing a prima facie case of obviousness. Having concluded that the examiner has not established a prima facie case of obviousness, we do not reach the rebuttal declaratory evidence discussed in appellants' brief (pp. 9, 16, 19-22 and 30-32) and reply brief (pp. 8 and 11).

The rejections of claims 17-36 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner alone or further in view of Stratagene are reversed.

OTHER MATTERS

The transitional phrases "comprising," "consisting essentially of" and "consisting of" are terms of art which define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. "Comprising" is open-ended and does not exclude additional, unrecited components or method steps, while "consisting of" is close-ended and excludes any component or step not specified in the claim. "Consisting essentially of" occupies a middle ground and limits the scope of a claim to the specified components or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. See e.g., the MPEP, 7th ed. (rev. 1, February 2000), at § 2111.03.

Here, the claims appear to use these terms in a non-traditional manner which gives rise to internal inconsistencies. For example, claim 17 recites an oligonucleotide which consists of a first segment which comprises, i.e., is open to the inclusion of, nucleotides over and beyond those of a specified a selected sequence, a second segment which consists of a sequence at least 90% homologous to another sequence, and optionally one or more noncomplementary sequences. Thus, the closed scope of the oligonucleotide of claim 17 is open to the inclusion of additional, unrecited nucleic acids and optional sequences.

As represented to us by appellants, this non-traditional term usage appears to have arisen at the suggestion of the examiner.[4] However, in view of the apparent inconsistencies arising from this non-traditional term usage, appellants and the examiner should review any allowable claims prior to issuance in light of the art-recognized definition

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[4] According to appellants,

> The first and second segments [of the claimed probes and probe sets] as defined constitute the only essential structural features of the optimized HTLV-1 probes. However, since a user can included additional "filler" sequence that is not complementary to HTLV-1 (and is therefore unlikely to impact hybridization) as described in the specification, the claims were originally written with the open claim language "comprising". In consultation with the Examiner of the predecessor application, it was considered preferable to employ the closed claim language "consisting of" and to specifically recite the noncomplementary sequence as an optional element. Applicants previously adopted the former Examiner's suggestions in an effort to expedite prosecution, and that language is reflected in the pending claims. [Emphasis added, brief, fn. 1.]

of "comprising," "consisting essentially of" and "consisting of" to ensure that claims of proper scope issue.

CONCLUSION

In conclusion, the decision of the examiner (1) to reject claims 17-33 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner is reversed, and (2) to reject claims 34-36 under 35 U.S.C. § 103(a) as being unpatentable over Urdea in view of Seiki and either Hogan or Ratner and further in view of Stratagene is reversed.

REVERSED

SHERMAN D. WINTERS)
Administrative Patent Judge)

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	)
	) BOARD OF PATENT
CAROL A. SPIEGEL	) APPEALS
Administrative Patent Judge	) AND
	) INTERFERENCES
	)
	)
	)
TONI R. SCHEINER	)
Administrative Patent Judge	)

Appeal No. 1997-2532
Application No. 08/427,569

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APPEAL NO. 1997-2532 - JUDGE SPIEGEL
APPLICATION NO. 08/427,569

APJ SPIEGEL

APJ WINTERS

APJ SCHEINER

DECISION: **REVERSED**

Prepared By:

DRAFT TYPED: 02 Jul 01

FINAL TYPED:

Paper No. 44

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RALPH R. WEICHSELBAUM, DENNIS E. HALLAHAN,
VIKAS P. SUKHATME, and DONALD W. KUFE

Appeal No. 1999-1458
Application No. 07/943,812

ON BRIEF[1]

Before WINTERS, WILLIAM F. SMITH, and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 3-21, 36, 38-41, 48-50 and 52-59, which are all the claims pending in the application.

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[1] Pursuant to appellants request (Paper No. 39, received September 18, 1998) an oral hearing for this appeal was scheduled for Tuesday, October 9, 2001. Appellants, however, waived (Paper No. 43, received October 2, 2001) their request for oral hearing. Accordingly, we considered this appeal on Brief.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. An isolated and purified DNA molecule comprising a radiation responsive enhancer-promoter operatively linked to an encoding region that encodes at least one polypeptide, other than CAT, that one desires to have expressed in a radiation responsive manner, which encoding region is operatively linked to a transcription-terminating region, wherein said radiation responsive enhancer-promoter comprises a portion of the CArG domain from –550 to –50 of an Egr-1 promoter or a c-jun promoter.

The references relied upon by the examiner are:

Hung et al. (Hung)	4,370,417	Jan. 25, 1983
Mark et al. (Mark)	4,677,064	Jun. 30, 1987
Brent et al. (Brent)	4,833,080	May 23, 1989
Orr et al. (Orr)	4,835,098	May 30, 1989

Johnsson et al. (Johnsson), "The c-sis Gene Encodes a Precursor of the B Chain of Platelet-Derived Growth Factor," The EMBO Journal, Vol. 3, No. 5, pp. 921-928 (1984)

Angel et al. (Angel), "The Jun Proto-Oncogene is Positively Autoregulated by Its Product, Jun/AP-1," Cell, Vol. 55, pp.875-885 (1988)

Bonthron et al. (Bonthron), "Platelet-Derived Growth Factor A Chain: Gene Structure, Chromosomal Location, and Basis for Alternative mRNA Splicing," Proc. Natl. Acad, Vol. 85, pp. 1492-1496 (1988)

Christy et al. (Christy), "A Gene Activated in Mouse 3T3 Cells by Serum Growth Factors Encodes a Protein With 'Zinc Finger' sequences," Proc. Natl. Acad, Vol. 85, pp. 7857-7861 (1988)

Ghosh et al. (Ghosh), "Cloning of the p50 DNA Binding Subunit of NF- κB: Homology to rel and dorsal," Cell, Vol. 62, pp. 1019-1029 (1990)

Moolten et al. (Moolten), "Curability of Tumors Bearing Herpes Thymidine Kinase Genes Transferred by Retroviral Vectors," Journal of the National Cancer Institute, Vol. 82, No. 4, pp. 297-300 (1990)

GROUNDS OF REJECTION

Claims 1, 3-21, 36, 48 and 52-55 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of nucleotide numbers because the frame of reference is not clearly defined.

Claims 1, 3-21, 36, 38-41, 48-50 and 52-59 stand rejected under 35 U.S.C. § 103 as being unpatentable over Christy or Angel in view of any one of Bonthron, Johnsson, Mark, Moolten, Hung, Orr, Ghosh or Brent.

We reverse and raise other issues for the examiner's consideration.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer[2] for the examiner's reasoning in support of the rejections. We further reference appellants' Brief[3], and appellants' Reply Brief[4] for the appellants' arguments in favor of patentability. We note the examiner entered and considered the Reply Brief.[5]

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[2] Paper No. 38, mailed July 14, 1998.
[3] Paper No. 37, received May 11, 1998.
[4] Paper No. 39, received September 18, 1998.
[5] Paper No. 40, mailed October 1, 1998.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

As set forth in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991):

> The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. See Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits.").

Furthermore, claim language must be analyzed "not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

According to the examiner (Answer, page 4) "[c]laims 1, 54 and 55 are indefinite in their recitation of nucleotide numbers because the frame of reference (i.e. which base is "0" or "1") is not clearly defined." In response, appellants argue (Brief, page 5) that:

> [A]s a matter of scientific convenience, the base numbering of upstream regulatory regions typically relates to the start of transcription for the corresponding gene. Thus, even if there were no information in the literature on the numbering for these particular genes, and no guidance in the instant specification as to what regions are encompassed by the recitation of "-550 to –50," the claims would, nonetheless, be clear. Those of skill in the art would understand the claims to include those residues that are 50 to 550 bases upstream of the translational start site, simply by convention.

With reference to page 14, "Scheme 1" of the specification, appellants argue (Brief, page 6) that this "convention is used in the instant specification." However, the examiner argues (Answer, page 7) that while "[a]ppellants argue that one skilled in the art would know that nucleotide '0' is the transcriptional start site ... the convention is that the transcriptional start site is nucleotide '1,' not '0'." In response, appellants argue (Reply Brief, page 4) "the 'conventional' numbering to which the examiner refers, where '+1' is the start, also used [sic] '-1' as one base before the start. Thus, '-550 to –50' is the same for both." We agree with appellants. We also note that in "SCHEME 1" of the specification (page 14) "+1" is defined as "0".

The examiner also finds (Answer, page 7) that "Angel et al. indicate that the jun gene has at least three transcriptional start sites. They state, '[t]he major start site of transcription was arbitrarily numbered +1' (Fig. 4) and later refer to 'two minor start sites' (p. 878, col. 1)." In response, appellants argue (Reply Brief, page 4), "Scheme 1 indicates the general position of the defined start site, if for no other reason, than the spacing of the six CArG domains." As we noted above, "SCHEME 1" of the specification (page 14) defines "+1" as "0." Therefore, regardless of the existence "minor start sites," Angel defined the "+1" site, this site to appellants specification is defined as "0" and is therefore the "frame of reference" from which –550 to –50 are determined.

Therefore, in our opinion, the claims reasonably apprise those skilled in the art as to their scope. Accordingly, we reverse the rejection of claims 1, 3-21, 36, 48 and 52-55 under 35 U.S.C. § 112, second paragraph.

THE REJECTION UNDER 35 U.S.C. § 103:

The examiner finds (Answer, bridging sentence, page 4) that Christy "disclose[s] DNA constructs comprising the Egr-1 ... promoter linked to the CAT reporter gene... [demonstrating] that a heterologous gene can be expressed under control of the Egr-1 promoter...." In addition, the examiner finds (Answer, page 5) that Angel "demonstrate[s] that a heterologous gene can be expressed under control of the c-jun promoter...." However, the examiner finds (id.) that "[n]either Christy et al. nor Angel et al. disclose DNA constructs in which the promoter is linked to a gene encoding a 'therapeutic' polypeptide."

To make up for the deficiency of Christy and Angel, the examiner relies (Answer, page 5) on any one of Bonthron, Johnsson, Mark, Moolten, Hung, Orr, Ghosh or Brent, which teach the coding sequence of various proteins. With this the examiner concludes (Answer, page 6) that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to link either of the promoters taught by Christy et al. and Angel et al. to any of the coding sequences disclosed by Bonthron et al., Johnsson et al., Mark et al., Moolten et al., Hung et al., Orr et al., Ghosh et al. or Brent et al., in order to express the coding sequence.

According to the examiner (Answer, page 8) a person "of ordinary skill in the art knew that any coding sequence could be linked to any promoter for expression of the coding sequence. It is obvious to substitute known equivalents for the same purpose, even if there is not an express suggestion to substitute one equivalent component for another...." On the surface, the examiner appears to make out a reasonable prima facie case of obviousness. We note that when the prior art recognizes two components to be equivalent, an express suggestion to

substitute one for another need not be present in order to render such substitution obvious. In re Fout, 675 F.2d 297, 301, 213 USPQ 532, 536 (CCPA 1982).

According to appellants (Brief, page 9), the examiner ignored their unexpected results. Specifically, appellants argue (Brief, pages 9-10) that "[t]here is no teaching or suggestion in the prior art regarding the radiation inducibility of the claimed constructs ... [t]he examiner has not disputed these facts and even admits that the radiation inducibility of the claimed constructs was nonobvious." To this the examiner argues (Answer, page 9), "[t]here is no evidence of unexpected results. Radiation inducibility is a previously unknown property of the jun and Egr-1 promoters, not an unexpected result of combining the promoters with any coding sequence other than CAT." Once again, on the surface, there is some merit to the examiner's argument. As set forth in In re Dillon, 919 F.2d 688, 693, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc):

> There is no question that all evidence of the properties of the claimed compositions and the prior art must be considered in determining the ultimate question of patentability, but it is also clear that the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a prima facie case. ... [In re Shetty, 566 F.2d 81, 86, 195 USPQ 753, 756 (CCPA 1977)]. Each situation must be considered on its own facts, but it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant.

In In re Shetty, 566 F.2d 81, 86, 195 USPQ 753, 756 (CCPA 1977), the court found that:

> Appellant merely shows that his novel compounds are appetite suppressants whereas the reference compounds are not so known. ... Presented with such an absence of comparative or other evidence with respect to the properties of the compounds and the claimed composition, we hold that [the] composition ... would have been obvious from and unpatentable over the prior art.

These cases appear to be consistent with the examiner's conclusion (Answer, page 11) that "[a]ppellants discovered that the promoters are ... induced by radiation. On the basis of this discovery, they wish to exclude others from using the promoters in combination with any coding sequence other than CAT, for any purpose. The [e]xaminer's interpretation of the law is that this is not permitted." But, if one looks under the surface, the facts of record in this case do not lead to the examiner's conclusion.

The claimed invention is drawn to "[a]n isolated and purified DNA molecule comprising a radiation responsive enhancer-promoter operatively linked to an encoding region that encodes at least one peptide, other than CAT...." According to the examiner (Answer, page 9), that the claimed promoter is radiation responsive is an inherent property of the promoter; it is not the "unexpected" result of combining this regulatory sequence (promoter) with a structural sequence other than CAT. We agree with this part of the examiner's analysis. However, the analysis does not end there.

In responding to appellants' arguments it appears that the examiner more fully develops his prima facie case of obviousness. According to the examiner (Answer, pages 8-9) "[t]hose of ordinary skill in the art knew that any coding sequence could be linked to any promoter for expression of the coding sequence. It is obvious to substitute known equivalents for the same purpose,

even if there is not an express suggestion to substitute one equivalent component for another." It is this statement, however, that illustrates the deficiency in the examiner's prima facie case. As we understand the examiner's reasoning, as a general proposition, it would have been obvious to substitute known equivalent coding sequences, or known equivalent promoters.

It is, however, not entirely clear on this record what the examiner may mean by equivalent coding sequences. Furthermore, we find that the examiner has not established that the coding sequences are "equivalent." Instead, the examiner finds (Answer, page 5) that each coding sequence encodes a different protein. Without a showing of equivalence the examiner has not established a prima facie case of obviousness.

That leaves the promoters. The examiner's position appears to be, since the promoters of either Angel or Christy are "equivalent" to the promoters set forth in the secondary references it would be obvious to substitute one for the other. The examiner, however, failed to demonstrate that any of the promoters used by the secondary references are in fact radiation responsive, and therefore "equivalent" to the promoter of either Angel or Christy. Stated differently, there is no evidence on this record demonstrating that the promoters of the secondary references are radiation responsive. Therefore, there is no evidence on this record that the Angel or Christy promoters are equivalent to the promoters of the secondary references. Without a showing of equivalence the examiner has not established a prima facie case of obviousness.

In contrast to the facts in evidence on this record, in Dillon, 919 F.2d at 692, 16 USPQ2d at 1900-01 there was an art recognized equivalence between the tri-orthoesthers of the primary reference and the tetra-orthoesthers of the secondary reference. In Shetty, cited in Dillon, the structural similarity between the prior art compound and the claimed compound was such that one would have expected the two compounds to possess similar properties; evidence of unexpected properties was not of record. On this record, there is no evidence that the prior art structural genes are equivalent to each other. Furthermore, there is no evidence that appellants' promoter is equivalent to the prior art promoters. In addition, appellants demonstrate that their promoter has an unexpected advantage over other promoters (such as those found in the secondary references); specifically appellants' promoter is radiation responsive.

On reflection, in our opinion, there is no suggestion for combining the teachings of the references relied upon by the examiner in a manner that would have reasonably led one of ordinary skill in this art to arrive at the claimed invention. The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On this record, the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. Accordingly, we reverse the rejection of claims 1, 3-21, 36, 48-50 and 52-59 under 35 U.S.C. § 103 as being unpatentable over Christy or Angel in view of any one of Bonthron, Johnsson, Mark, Moolten, Hung, Orr, Ghosh or Brent.

OTHER ISSUES:

We offer the following observations for the examiner's consideration.

I. Tsai-Morris:

Upon review of this administrative file, we note that Tsai-Morris[6] appears to correspond to at least claim 1 of appellants' claimed invention. Specifically, Tsai-Morris teach "the isolation of a mouse Egr-1 genomic clone, its intron-exon structure and 935 bp of 5' flanking sequence. The gene spans about 3.8 kb and consists of 2 exons and one 700 bp intron." See abstract. In addition, Tsai-Morris teach (id.) that this clone contains "five elements whose sequence is nearly identical to the inner core 10 nucleotide region (CCATATTAGG) of the c-Fos serum response element...." We note that appellants specification defines the claimed CArG domain as a "serum response or $CC(A/T)_6GG$" domain. In addition, we note that this DNA molecule is expected to encode at Egr-1, which is a polypeptide other than CAT.

Upon return of this application, the examiner should take a step back and determine whether Tsai-Morris anticipates the claimed invention. In this regard, we note as set forth in In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990):

> discovery of an unobvious property and use does not overcome the statutory restraint of section 102 when the claimed composition is known. While Spada's position is that his polymers are not anticipated by the polymers of Smith because their properties are different, Spada was reasonably required to show that his polymer compositions are different from those described by Smith. This burden was not met by simply including the assertedly different properties in the claims. When the claimed compositions are not

[6]Tsai-Morris et al. (Tsai-Morris), "5' flanking sequence and genomic structure of Egr-1, a murine mitogen inducible zinc finger encoding gene," Nucleic Acids Research, Vol. 16, No. 18, pp. 8835-8846 (1988).

novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

II. Written Description:

As set forth in UC v. Eli Lilly and Co., 119 F. 3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Furthermore, Lilly 119 F.3d at 1568, 43 USPQ2d at 1406, indicates, "[a] definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." In this regard, we note, for example, that unlike appellants' claim 1, wherein the radiation responsive enhancer-promoter comprises a portion of the Egr-1 or c-jun promoter, claims 56-59 are broadly drawn to any "isolated and purified DNA molecule comprising a radiation responsive enhancer promoter."

Upon return of this application, the examiner should take a step back and determine whether appellants' specification provides an adequate written description of any "isolated and purified DNA molecule comprising a radiation responsive enhancer promoter" as set forth in claims 56-59.

REVERSED

Sherman D. Winters)
Administrative Patent Judge)
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William F. Smith	)
Administrative Patent Judge	) APPEALS AND
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X. RELATED PROCEEDINGS APPENDIX

None